THERAPY OF INFECTIONS

*Transcription of a Panel Meeting**

DAVID E. ROGERS . . . Moderator

Associate Professor of Medicine, Cornell University Medical College;
Head of Division of Infectious Diseases, Associate Attending Physician,
The New York Hospital

Panel Members

AARON D. CHAVES

Assistant Professor of Clinical Medicine, Cornell University Medical College;
Supervisor of Clinics, Bureau of Tuberculosis, Department of Health,
City of New York

EDWIN D. KILBOURNE

Associate Professor and Director, Division of Virus Research,
Department of Public Health and Preventive Medicine, Cornell University Medical College;
Associate Attending Physician, The New York Hospital

RALPH R. TOMPSETT

Associate Professor of Clinical Medicine, Cornell University Medical College
Visiting Physician, Bellevue Hospital

THEODORE E. WOODWARD

Professor and Head, Department of Medicine, School of Medicine, University of Maryland;
Physician-in-Chief, University Hospital, Baltimore, Maryland

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MODERATOR DAVID E. ROGERS: Ladies and Gentlemen, the subject before us is an extremely broad one. We have therefore agreed to confine our remarks to certain infections which have gained in importance in recent years and to areas of therapy undergoing rapid change.

The treatment of staphylococcal infections has been receiving increasing attention. Dr. Woodward, are you admitting more patients with staphylococcal infections to your hospital in Baltimore?

DR. THEODORE E. WOODWARD: It is my conviction that we are encountering more patients with staphylococcal disease in the hospital than heretofore. Staphylococcal disease is becoming a hospital problem, more resistant strains are being encountered increasingly often and as patients leave the hospitals they must be exposing the general population to penicillin-resistant strains. Lacking any specific data on this point my answer, purely a conviction, is yes.

MODERATOR ROGERS: Let me make my question more specific. Were more patients admitted with acute staphylococcal infections in 1956 than there were, for example in 1936? In other words, are more patients developing staphylococcal infections *outside* the hospital than in the pre-antimicrobial era?

DR. WOODWARD: It is my opinion that the problem outside the hospital is greater. Patients are being encountered with staphylococcal problems such as furuncles, carbuncles, cellulitis, sepsis, endocarditis and pneumonia. Furunculosis with cellulitis and endocarditis seem to me to be greater in incidence, so it is my belief that more patients with staphylococcal infections are being admitted directly from the outside.

MODERATOR ROGERS: Dr. Tompsett, are you admitting more staphylococcal infections to Bellevue than you did before we had antimicrobials?

DR. RALPH TOMPSETT: I don't know whether I can answer specifically with regard to Bellevue, not having been there all of these past 20 years, but this is one question I should like to be able to answer definitely. There is no question that more of our waking hours are spent in the management of staphylococcal infections than ever before and the time involved is increasing every year. My impression would be that we are seeing more patients with serious staphylococcal infections admitted to the hospital than previously, but probably some sort of an average is struck in that there may be more infections occurring but

with some of them being handled outside the hospital. Therefore, although we see about the same number, they are more serious. I just don't think we know the answer to that question.

MODERATOR ROGERS: Do you have any comments on this problem, Dr. Chaves? Dr. Kilbourne?

DR. EDWIN D. KILBOURNE: I would like to give three answers. The first is, I don't know. The second answer is that I have the impression that staphylococcal infections are not increasing as problems on admission, on total number of patients admitted, and the third answer is to refer specifically to a four year experience at Tulane. During that brief time we had some opportunity to get figures on this and we were not impressed by an increased incidence. I can add to this the comparative experience of all the clinicians who had been in that environment for a long time, and they, too, felt there was no particular increase of the problem on admission. I would, however, certainly agree with Dr. Tompsett, that a great deal more of our time seems to be occupied with the management of these patients.

MODERATOR ROGERS: I am interested in the apparent discrepancies between Baltimore and New York. We have recently analyzed the incidence of admission to New York Hospital for staphylococcal infections, comparing the pre- and post-antimicrobial eras. We have found no increase in the incidence of staphylococcal disease as a cause of admission to New York Hospital, but have found that staphylococcal infections arising *within* the hospital are an increasing problem and have caused us serious difficulty.

DR. WOODWARD: Let me qualify my statement to the extent that I think our problem is greater, although we have not made a careful analysis since 1936. My impression is probably not an accurate appraisal of the situation.

MODERATOR ROGERS: *Dr. Tompsett, what is the clinical significance of antimicrobial resistant staphylococci? Is* in vitro *resistance of importance in the treatment of these infections?*

DR. TOMPSETT: I think it is of very great importance, particularly with regard to the penicillin resistance. If one has, let us say, two patients with the same type of staphylococcal infection and one is susceptible to penicillin and the other one is not, but is susceptible to other drugs, penicillin can be used. We much prefer to use it and when usable, it seems to be a very good drug in the treatment of

staphylococcal infections. With the other drugs, even though the susceptibility tests may indicate that the organisms are susceptible, the results are not nearly as good, so that penicillin resistance is certainly of major importance. I am sure resistance to other drugs is also of major, but perhaps not of such great importance.

MODERATOR ROGERS: *Dr. Woodward, do you believe that penicillin resistant staphylococci are more virulent than sensitive strains? In other words, are we creating a group of extremely vicious antimicrobial-resistant staphylococci that are capable of producing more severe infections than we used to see before we had antimicrobials?*

DR. WOODWARD: My impression is that we have created a group of organisms which are causing diseases that are more difficult to manage.

MODERATOR ROGERS: *Do they cause worse disease?*

DR. WOODWARD: I think the disease is the same; whether it is endocarditis or any other localized infection. It seems to be the same staphylococcal disease. We see more of it, and as Dr. Tompsett has indicated it requires more of our time.

MODERATOR ROGERS: *Dr. Kilbourne, do you think resistant staphylococcal infections are more destructive than infections due to sensitive strains?*

DR. KILBOURNE: My experience has, of course, been largely in the antibiotic era, but I think comparative mortality rates indicate that severe staphylococcal infections are still severe staphylococcal infections. One of the most difficult things to prove is the actual virulence of an organism, even when dealing with experimental infections and experimentally controllable situations. I think it is an almost unanswerable question.

MODERATOR ROGERS:. *Dr. Tompsett, how do you manage patients with serious staphylococcal bacteremia?*

DR. TOMPSETT: I would like to date this [October, 1956, Ed.] because I might give a different answer next week. As of today, I think the first thing we try to do whenever possible is to attack this problem surgically if there is anything that can be done surgically. When we are dealing with one that is manageable surgically we have considerably better results, entirely aside from the question of sensitivity to antimicrobial agents. If a staphylococcal infection is severe, at the present time we assume that this is going to be penicillin resistant and we start the patient on another drug. I believe

at this time erythromycin would be drug No. 1. We generally use two drugs in treating patients with severe infections largely because of the difficulty in management. We know that no one drug is sufficiently good so that, by and large, we use erythromycin and chloramphenicol to initiate therapy. Then we get our cultures, do our sensitivity tests and, if found to be susceptible to penicillin, we always use penicillin.

MODERATOR ROGERS: I am interested to learn that you do not initiate therapy with penicillin.

DR. TOMPSETT: Unless the patient has osteomyelitis. In such instances we have found so far that most of these infections are due to penicillin-susceptible organisms, for some reason which I am unable to figure out. But with osteomyelitis we start the patient on penicillin.

MODERATOR ROGERS: *How much penicillin do you use?*

DR. TOMPSETT: We use about 5 million units per day.

MODERATOR ROGERS: *Dr. Woodward, how do you handle patients with acute staphylococcal sepsis where the sensitivity of the organism is unknown when you first see them?*

DR. WOODWARD: I think our rule of thumb is similar to Dr. Tompsett's and for local infections we emphasize the time honored measures. When the local infection has not responded and shown evidence of progression we are inclined to employ a Group 2 antibiotic, such as erythromycin or chloramphenicol. Given a patient with clinical signs of bacteremia with or without signs of endocarditis, we naturally hope that the organism is penicillin-sensitive. Under these conditions penicillin is our first choice. If the organism on *in vitro* testing by the tube dilution method is not too sensitive, we give penicillin but we are inclined to supplement the penicillin regimen with streptomycin. That is the general rule that we have been using in patients who have staphylococcal disease with possible bacteremia, when the heart valves are conceivably involved. We tend to hit quite hard with penicillin.

MODERATOR ROGERS: I believe the setting in which the infection arises has, in part, governed our initial therapy. When patients with acute staphylococcal infections are admitted from the outlying community where they have had no contact with doctors or antimicrobials —this incidentally applies to a fair number of children with osteomyelitis—we have found that their infections are generally due to penicillin susceptible staphylococci. We thus start therapy in this group with large amounts of penicillin. When we have had staphylococcal infec-

tions develop within the hospitals, the reverse has been true. These infections are usually due to penicillin resistant staphylococci and we have thus been inclined to use other drugs in initiating therapy.

DR. KILBOURNE: May I dissent from what seems to be a majority opinion and dissent with the idea of addressing a question to the panel for my own information. It has been my practice always to include penicillin in the management of any patient who has staphylococcal disease and who exhibits systemic signs of toxicity, on the assumption that he should be treated as a case of endocarditis until proved otherwise and therefore be given what is optimal therapy. My reason for always using penicillin is that regardless of where the patient comes from, outside the hospital or inside the hospital, I think all of us have had sufficient experience with patients who apparently show wide discrepancy between the *in vitro* sensitivity of the organism and the results obtained by drug therapy in the patient. There are patients whose clinical pattern of response to penicillin varies in a manner which does not correspond at all to the *in vitro* sensitivity. Regardless of the fact that a highly "resistant" staphylococcus is present they get well with penicillin and not without it. These cases are somewhat difficult to document. I imagine when we get down to statistics, we each may have seen three of four cases of this sort. But I would like to provoke a little discussion on this point and ask why, if this is true or accepted, we don't always give penicillin?

MODERATOR ROGERS: *Dr. Tompsett, I believe you indicated that you don't always start out with penicillin?*

DR. TOMPSETT: Until a year ago we did exactly what Dr. Kilbourne has just described. We acted on the basis of experience in patients with severe staphylococcal infections who were treated with penicillin and streptomycin and who had favorable clinical results, even though the *in vitro* sensitivity tests indicated that they would not respond. We have been treating these patients with penicillin and streptomycin right from the very beginning. I would like to add that this procedure is still followed where there is any suggestion of endocarditis, as Dr. Woodward has mentioned. This of course, does not make much sense from our knowledge of the *in vitro* tests but as Dr. Kilbourne has indicated, the experience is very limited. Nobody sees very many of these patients and even though we believe there may be considerable virtue in this combination, we are at present giving a trial to the other one,

which does make sense from the standpoint of *in vitro* sensitivity tests. I believe that the difference of opinion expressed here only reflects the fact that none of these regimens is really ideal. So it is a matter of trial and error in a situation where no one therapy can be relied upon.

MODERATOR ROGERS: *Do you believe there could be positive harm in using penicillin except in the sense that one is using a drug that may be ineffective?*

DR. TOMPSETT: I think there is at least the possibility of doing positive harm, not from the standpoint of the microorganism but from the standpoint of reactions in the patient. I have had the misfortune of administering two or three drugs and frequently ending up with a patient who exhibits a hypersensitivity reaction to one of them and not knowing which one is responsible. This is an unfortunate clinical situation if more than one drug is given and especially so if you are giving three. This is the only disadvantage that I can see and it is not too serious a one.

MODERATOR ROGERS: *This brings up a question that I would like to explore further. All of you have mentioned the use of combined therapy in treating staphylococcal infections. What evidence do we have that combined therapy is appropriate? Dr. Woodward, can you defend the use of more than one agent in this situation?*

DR. WOODWARD: As a general rule we do not like combination therapy. We prefer one antibiotic in a regimen for some of the reasons that Dr. Tompsett mentioned. Some patients do not do well on one drug alone and one soon discovers that the one drug, even if given in very significant doses, is not doing the job. I can recall a patient with staphylococcal endocarditis who required 18 million units of penicillin a day to keep her blood stream free of the organism and to keep her free of clinical signs of illness. It was difficult to administer this much penicillin over a period of time. However, with appropriate antibiotic sensitivity testing (tube dilution method), it was shown that Terramycin acted synergistically for this particular strain. Terramycin in that particular patient combined with 10 million units of penicillin daily effected a cure.

In another patient I insisted upon giving massive penicillin treatment for staphylococcal endocarditis. The patient had been receiving a combination of streptomycin and chloramphenicol and seemed to be making a slow response. Fortunately the initial strain had been saved,

and when tested in the laboratory it was shown that this was potentially a winning combination. I was wrong in my stand, for this patient did not require penicillin in spite of the creed that we usually adhere to: that penicillin is absolutely required for endocarditis. This patient recovered on streptomycin and chloramphenicol therapy. I do not think there is any basic dissent from the panel's view of treatment of staphylococcal sepsis, with or without endocarditis. I do think that we concur in believing that the problem must be evaluated in the individual patients who, by their reactions, present incontrovertible evidence of results. The patient himself is a pretty good sensitivity test as to what is happening.

MODERATOR ROGERS: *I notice that none of you have voiced concern regarding the development of antimicrobial resistance of staphylococci in a lesion under treatment. I would like to poll the panel on this point: have any of you ever witnessed a staphylococcus which increased in resistance to the drug or drugs which were being given during the treatment of a serious staphylococcal infection?*

DR. TOMPSETT: I have seen this occur with two drugs, streptomycin and erythromycin.

MODERATOR ROGERS: *How about you, Dr. Woodward?*

DR. WOODWARD: At the moment I can recall one instance with erythromycin.

DR. KILBOURNE: With erythromycin but not penicillin.

MODERATOR ROGERS: *Dr. Chaves, do you have any comment on that?*

DR. AARON D. CHAVES: No.

MODERATOR ROGERS: This seems to me an important point. I think we sometimes talk loosely about the dangers of increasing resistance of microorganisms *under therapy*. It has been our experience that staphylococci present in closed infections like endocarditis do not change in penicillin susceptibility during treatment even when therapy is inadequate and relapse occurs.

Dr. Woodward, how do you treat staphylococcal pneumonia in Baltimore and how long do you continue therapy?

DR. WOODWARD: The last patient with staphylococcal pneumonia whom we treated had measles and was given penicillin as a prophylactic measure. Infection of the lung developed during penicillin therapy. The patient made a very adequate response to chloramphenicol. We are using chloramphenicol rather freely in the treatment of staphylococ-

cal disease, as well as erythromycin.

MODERATOR ROGERS: *Dr. Tompsett are you seeing more staphylococcal pneumonia than before we had antibiotics? This has recently been reported in the British literature.*

DR. TOMPSETT: I believe this is such an uncommon disease that one's experience influences his judgment greatly. It does appear though, that there are now more cases of staphylococcal pneumonia on the pediatric wards than were seen in the past. While this is a relatively frequent problem in that department it is so rare in adults that the figures on incidence that any one person could collect would, I think, be almost meaningless.

MODERATOR ROGERS: *How long do you continue antimicrobial therapy in serious staphylococcal infections, Dr. Tompsett?*

DR. TOMPSETT: We are treating these patients for a long time, a minimum of six weeks if they have a very good response and we usually prefer to continue treatment for about that same length of time after they have obviously started to respond.

MODERATOR ROGERS: *What are your reasons for such extended treatment?*

DR. TOMPSETT: I think the principal reason is that these are patients in whom we never know whether or not endocarditis is present. That is the first thing. We know that the endocarditis must be treated for a long period of time. The second reason is, we have had the experience of treating patients who seemed to respond very well, when treated for two or three weeks and then had them relapse after stopping treatment. This happens even in such diseases as osteomyelitis. We have not given this short term treatment for quite a few years now because of this experience, but certainly relapse and the appearance of metastatic abscesses occur frequently enough to persuade us that all of these patients should have long term therapy.

MODERATOR ROGERS: *Dr. Kilbourne, do you have any difference of opinion?*

DR. KILBOURNE: No, only to emphasize how difficult it is to set any hard and fast rules in these situations because of the limited number of cases which we see and the wide variation in this particular disease, depending upon the number of peripheral foci. Some time ago, I rather arbitrarily decided to continue treatment for at least a month after defervescence or after the disappearance of staphylococci from the

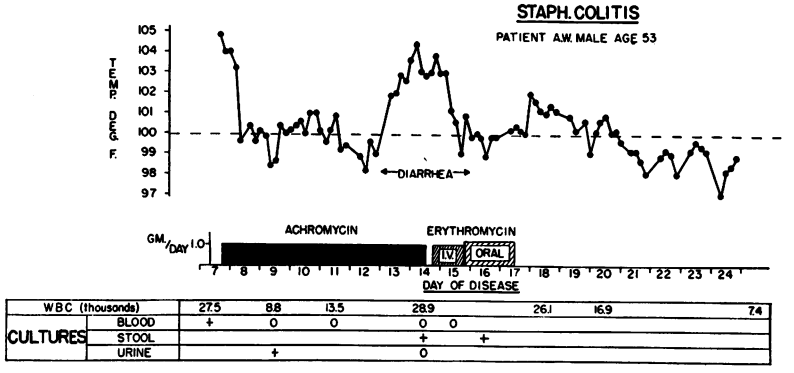

Fig. 1

blood culture. My follow-up of this regimen is inadequate.

MODERATOR ROGERS: *We have recently heard a great deal about staphylococcal enterocolitis as a hospital problem. Dr. Woodward, would you tell us a bit about your experience with this syndrome and how you handle it?*

DR. WOODWARD: I have a slide demonstrating the case record of a patient with this syndrome, if you care to see it.

MODERATOR ROGERS: *Please show it.*

DR. WOODWARD: This patient (Fig. 1) was undergoing treatment for pneumonia during the course of which diarrhea, abdominal pains and shock ensued. An alert house officer made a fecal smear and was able to establish the presence of staphylococcal disease. The patient did quite well on changing the therapy to erythromycin. We have had very few cases. I can recall another patient being treated for pneumococcal meningitis who developed colitis. As we all know this entity occurred long before antibiotics were in clinical use.

MODERATOR ROGERS: *Do you believe that staphylococci were the etiologic agent then?*

DR. WOODWARD: Perhaps there are some in this room who had the opportunity to hear Dr. Ivan Bennett speak before the Association of American Physicians in May of this year. Dr. Bennett presented the case record of a patient who had been operated upon at the Johns Hopkins Hospital in 1893 by Dr. John M. T. Finney. The patient developed colitis postoperatively. In those days this syndrome was called diphtheroid colitis. Dr. Bennett and his associates reexamined the

old preserved tissues and with appropriate staining techniques demonstrated staphylococci on the mucosal surface of the colon.

MODERATOR ROGERS: I think that this is an important point. We have "rediscovered" this disease entity recently. Perhaps it is on the increase but staphylococcal enterocolitis clearly occurred before antimicrobials entered the picture.

Dr. Tompsett, why do patients with enterocolitis die and how should this disease be managed?

DR. TOMPSETT: Too many answers I am afraid. They may die in shock. They may die as a result of the extreme fluid loss before there is sufficient recognition of what is going on. This happens too frequently. They also may die of any of the causes associated with staphylococcus septicemia—endocarditis or metastatic abscesses.

MODERATOR ROGERS: I might summarize briefly before turning to other areas. There is disagreement on the current incidence of staphylococcal infections. Our experience here in New York has led us to believe that staphylococcal infections have not increased as a *cause* of hospital admission but have increased as an intrahospital problem. We appear, in a sense, to have recreated the old puerperal fever wards. Many patients come in for surgery or with debilitating medical illnesses but free of infection and then develop serious staphylococcal infections due to resistant microorganisms. Dr. Woodward believes that perhaps we are admitting more staphylococcal infections than in the past from the outside community.

I think the panelists are agreed that staphylococcal infections probably remain unchanged in virulence. Infections due to resistant strains have gained prominence because of our inability to treat them effectively.

Most of the panelists are agreed that penicillin is the drug of choice when dealing with penicillin-sensitive strains and indeed, in a number of staphylococcal infections, even though they appear resistant in the test tube.

Erythromycin and chloramphenicol have been used in infections thought to be penicillin-resistant from their origin and indeed, Dr. Tompsett is now initiating therapy with these two drugs.

Dr. Woodward pointed out that the patient is a good sensitivity test in himself; if he is clearly responding, the antimicrobials in use should be continued despite laboratory evidence of resistance.

All are agreed that treatment should be continued at high dose levels for a long period of time because of the high relapse rate and development of metastatic abscesses. Dr. Tompsett recommends a minimum of six weeks.

Most of us are not seeing a great deal of staphylococcal enterocolitis. When this disease does occur it is frequently accompanied by shock and great fluid loss. Treatment includes its prompt recognition, withholding broad-spectrum regimens, rapid fluid replacement and the use of erythromycin or novobiocin.

We might turn now to the treatment of rickettsial infections. We have Dr. Woodward with us who has done a great deal of work in this area. Dr. Woodward, how much of a problem are rickettsial infections for us here on the East Coast? Are these infections common or are we talking about a fairly exotic disease?

DR. WOODWARD: As you see, Dr. Rogers is a gentleman because he asked me a statistical question with respect to staphylococcal disease and I feel that I did not do well with it. He is providing an opportunity to discuss more familiar terrain. No, I don't think we have a great incidence of rickettsial disease. We are rapidly going out of business with Rocky Mountain spotted fever in Maryland, the antibiotics are so effective. Physicians treat the patients at home. We are fortunate if we see two or three hospitalized cases a year. There are a few cases of spotted fever to be seen on Long Island. In this city you see some Brill-Zinsser's disease and it is interesting that these patients seem to be concentrated in certain of your excellent New York hospitals. We are dealing largely with a family of infections that are of more importance in other parts of the world than they are in the United States.

May I take a few minutes to summarize certain data pertinent to the rickettsioses?

MODERATOR ROGERS: Please do.

DR. WOODWARD: I should like to show a few slides. The first shows a group of rickettsiae in their intracellular habitat (Slide). These microorganisms find their way throughout the vascular system and choose the endothelial cells as a favorable site. The term "endovasculitis" is adequate to describe the anatomical lesion in patients with typhus fever, Rocky Mountain spotted fever and scrub typhus fever.

Insofar as the management of these diseases with antibiotics is concerned, the physician has been very fortunate because since 1948

TABLE I—RICKETTSIAL DISEASES—1948-1953

Disease	*Drug*	*No.*	*Deaths*
RMSF	Chloramphenicol	43	0
RMSF	Terramycin	9	0
RMSF	Aureomycin	5	0
Murine	Chloramphenicol	12	0
Murine	Terramycin	1	0
Brills	Aureomycin	1	0
Scrub	Chloramphenicol	274	0
	Total	345	0

he has had a group of effective antibiotics with high specificity of action for the rickettsiae. The antibiotics act as rickettsiostatic rather than as rickettsiocidal or killing agents. It will be noted that in the University Hospital in Baltimore, for the 15 year period 1930 to 1945, there were 85 patients with spotted fever who spent about 16 days each in the hospital. The fatality rate was 23 per cent. By contrast, treatment with various of the antibiotics, chloramphenicol and the tetracycline group, has virtually eliminated mortality. Fatality in this disease should not occur. The patient's temperature returns to normal levels two or three days after beginning therapy and the patient feels much better prior to defervescence.

Perhaps there will be time for a word with respect to the use of steroids in combination with specific chemotherapeutic agents.

(Slide) In this slide (Table 1) is summarized the clinical experience for the period 1948 to 1953. In a series of 345 cases of various rickettsial diseases, there were no fatalities. There is little significant difference between the therapeutic effect of chloramphenicol and the tetracyclines. They are all amazingly good.

(Slide) We should emphasize two problems of treatment. The first concerns the administration of the antibiotic to a patient who has had the disease for approximately a week or less. In that instance the antibiotic is enough. Such patients recover with reasonably good supportive care. However, in patients first seen late in the illness when the vascular changes are more pronounced, specific therapy is not enough. These patients require good supportive care as well, and good supportive care means support to the circulatory system. This includes both adequate

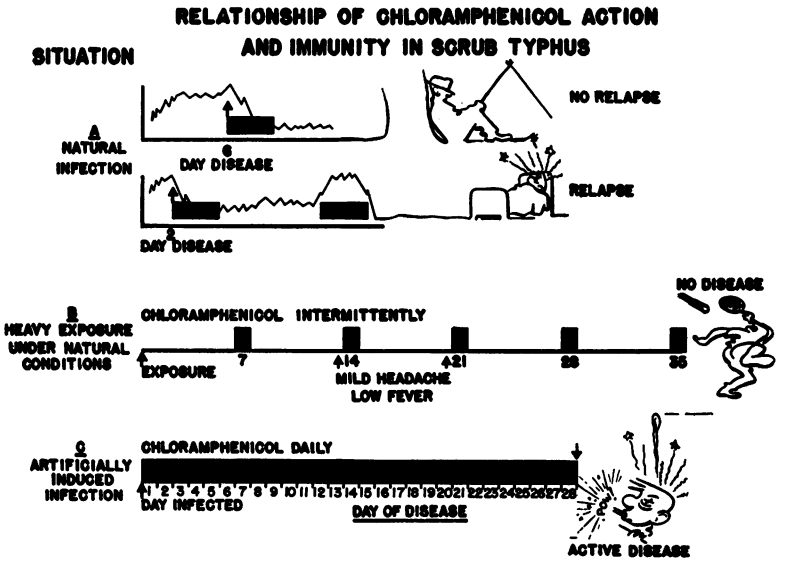

Figure 2.—Relationship of chloramphenicol action and immunity in scrub typhus. Reproduced from Fig. 8 in Woodward, T. E. and Parker, R. T. Clinical application and mode of action of antibiotics in rickettsial and virus diseases, in "International Symposium on Dynamics of Virus and Rickettsial Infections" by Hartman, Horsfall and Kidd. Copyright, 1952. Blakiston Div., McGraw-Hill. (Reproduced by permission.)

protein intake and electrolyte balance. Ordinarily, if one treats the patient with an antibiotic, the temperature returns to normal in a short time. Occasionally there is a relapse about which there will be a word in a minute.

As mentioned previously, corticoids have been used. Cortisone has been administered to patients with Rocky Mountain spotted fever and to patients with typhus fever. Cortisone or its analogues are not needed as a routine expedient but occasionally in an extremely toxic patient one may bring about considerable improvement within 24 hours. One would not hesitate to use steroids in conjunction with antibiotics in the severely ill case but not as a routine measure.

(Slide) I mentioned the problems of relapse. This slide (Fig. 2) gives a summary of the results of approximately three years' experience with the rickettsial disease, scrub typhus, or tsutsugamushi disease as it is known in Japan. Under situation A, note that when the patient is treated for his diseases on about the sixth day, which is the usual time

that the clinical diagnosis is established concurrently with the appearance of a rash, the antibiotic results in prompt defervescence. Moreover a patient treated at this stage does not relapse. In scrub typhus patients, (but rarely in spotted fever, I have only seen it in one or two instances) when the disease is detected quite early, one is able to make an accurate diagnosis. With treatment, the defervescence is prompt but the patient may relapse and usually the relapse occurs about eight days after the antibiotic has been stopped. One would surmise that had antibiotic treatment been extended recrudescence might have been prevented. Under situation C are the results of a human experimental trial conducted by the United States Army typhus team in Malaya under the general direction of Dr. Joseph E. Smadel. Human volunteers were infected with the agent of scrub typhus and given chloramphenicol daily for 28 days. The incubation period of typhus is approximately seven days, the anticipated course of the disease two weeks, and in this trial the antibiotic was given for seven additional days for good measure. The antibiotic is suppressive in its mode of action, so that on stopping the drug, under these conditions, active signs of full blown disease develop in most instances.

Now consider Situation B, when the antibiotic has been administered on an intermittent basis. During the rest periods there may be unapparent disease consisting of moderate headache, low grade fever and rickettsia may be isolated during the treatment interval. Under this regimen of intermittent therapy for about five weeks, there will be clinical suppression of the acute illness and the patient will develop some measure of immunity, at least enough to keep him from developing the active disease.

The studies just cited did demonstrate that the timing of antibiotic treatment exerts some influence upon the rate at which immunity develops. The term "immunity" is used in a broad sense.

(Slide) One final slide. Colonel William Tigertt reported this work on Q fever at the May 1956 meeting of the Association of American Physicians.

A trial using Rickettsia burneti or the agent of Q fever was conducted in human volunteers. It may be seen that as the infecting dose was increased the incubation period became shorter. Moreover, as the infecting dose increased, more of the subjects developed detectable clinical disease as well as serologic evidence for the presence of disease.

It is of interest that the antibiotics influence the course of patients with Q fever, similar to that in scrub typhus. In this study, when these infected subjects were given Terramycin within the first or second day of the active disease, subsequent relapse did not occur. This differs from the comparable situation in scrub typhus. However, when the antibiotic was given soon after infection, the antibiotic merely prolonged the incubation period. Such subjects treated with the antibiotic for five days beginning immediately after administration of the infecting dose, ultimately developed the disease.

One additional point is of considerable interest. The administration of killed Q fever rickettsia soon after the administration of viable Q fever rickettsia was sufficient in some instances to keep the patient from developing active disease. In other words, some volunteers developed resistance from the killed microorganisms before the incubation period of the viable organisms had been spent.

In summary, we may conclude that as far as the practical management of the rickettsial infections is concerned, the antibiotic drugs are amazingly effective. In the late case, it is not sufficient to make a diagnosis of rickettsial infection and prescribe an antibiotic. It is necessary to provide adequate circulatory support. These tissue changes provide a challenge in the rickettsial diseases. It is necessary to define the changes within endothelial cells and to determine why the capillaries are so permeable. Knowledge of the alterations at the tissue level is needed for more comprehensive management of the seriously ill late patient.

MODERATOR ROGERS: Thank you, Dr. Woodward.

Microorganisms in the psittacosis ornithosis group have now been reclassified as rickettsiae. Is there any clinical way we can differentiate specific rickettsial pneumonia from viral "atypical" pneumonia, Dr. Kilbourne?

DR. KILBOURNE: It may be possible to do so, but I can't. We have been fooled even in New York City with patients in whom we had no reason, on epidemiological grounds, to suspect psittacosis infection. We have treated them as atypical pneumonia, meaning we do nothing for them, and then have been astounded retrospectively to find they have developed complement fixing antibodies against psittacosis agents. I think there are some points, however, that might be helpful. Certainly most cases of psittacosis with pneumonic involvement are more severe

infections than most cases of the nebulous entity that we call atypical pneumonia, which is almost unquestionably a number of entities of probable viral etiology. I believe psittacosis infections differ principally in that they tend to be more acute, more precipitous in onset. They are, in my experience, almost invariably attended by rather racking headache and severe constitutional reaction. These signs may be seen at times in the virus sort of atypical pneumonia but not in most cases, and usually the chief helpful distinguishing feature on clinical grounds is the rather protracted and indolent course of atypical pneumonia of virus etiology. The onset tends to occur very gradually after preceding upper respiratory tract signs. In my experience the onset of psittacosis is more rapid.

MODERATOR ROGERS: *Do you thus treat very sick patients with a viral-like pneumonia as if they had psittacosis?*

DR. KILBOURNE: I usually do, for the further reason that I think, though we speak much of atypical pneumonia as being a virus disease and whether or not we question the efficacy of broad-spectrum antibiotics in its management, there is a theoretical basis for assuming that at least part of the severe illness is related to possible concurrent or intercurrent bacterial infection. The pathology of the disease is accompanied by bronchiolar excavation. The fatal cases always show some evidence of bacterial infection. So I think on this ground as well as on the basis of the very great difficulty in distinguishing, at least in my mind, the syndrome from psittacosis, that it certainly would be proper to treat with antibiotics.

MODERATOR ROGERS: *What antimicrobials do you use?*

DR. KILBOURNE: I believe it probably is analogous to the rickettsial situation in that it does not matter a great deal which one is used. I have had more experience with oxytetracycline than anything else and this has proved efficacious,—a gram a day is usually sufficient. However, it seems to be necessary to continue treatment for at least three weeks if febrile relapse is to be avoided. This again is on the basis of very slight experience but with cases authenticated by laboratory documentation.

MODERATOR ROGERS: *Are there any other viral diseases that respond to specific antimicrobial therapy? Again, Dr. Kilbourne, is there anything this audience should know about the management of the common cold or influenza?*

DR. KILBOURNE: By the very nature of our definitions these days I believe all viruses which are not responsive to the present day antimicrobial agents can be excluded automatically from consideration in discussions of this sort. As a matter of fact, the impetus for reclassifying the larger viruses of the psittacosis group arose largely from the fact that they respond to antimicrobial agents. So the sad fact remains that we do not have any specific chemotherapy or antimicrobial therapy available for the smaller viruses.

Just a brief word about the use of antimicrobial agents or antibiotic agents in such virus diseases as influenza of the present day [1956 —not the Asiatic Type A variant Influenza of 1957.—Ed.] and that is that I believe the use of these agents is definitely not indicated unless one is dealing with older people or people in whom pulmonary complications might be anticipated. The few people who die in the course of influenza epidemics are usually in the older age groups of the population or are those with previous lung disease of some sort.

We had practical experience with this in a large scale outbreak in Fort Monmouth in 1947. There we had the problem of deciding whether to treat everybody with prophylactic antibiotic therapy or whether to treat nobody. Because of the shortage of medical officers we were concerned about not using antimicrobial prophylaxis, but nevertheless we decided to follow this course and found that in this group of young, previously healthy adults, that we had no trouble. There were some bacterial complications but I think this was an experience which has been supported by a number of other studies. My belief is then, that in general there is no indication,—with the possible exception of measles in children which is severe,—for the use of antimicrobial therapy with the virus diseases caused by the smaller viruses.

MODERATOR ROGERS: *Dr. Chaves, we have kept you very quiet. We want to consider briefly the therapy of tuberculosis and learn of any recent changes in the management of this disease. Is tuberculosis a vanishing disease? Are you seeing less tuberculosis here in New York City than heretofore?*

DR. CHAVES: Basically we are still seeing such large numbers of people with active tuberculosis and recent tuberculosis that from a practical point of view the answer is, it is still very much with us.

MODERATOR ROGERS: *How are you handling new cases of minimal tuberculosis at this time, Dr. Chaves?*

DR. CHAVES: If the cases are minimal and active, the chances are one is faced with the problem of what to do in individuals whose diagnoses still have not been confirmed bacteriologically. If we assume that there is roentgenographic evidence of an infiltrate which is believed to be of recent origin and looks like tuberculosis in an individual whose tuberculin test is positive, the chances are there will not be bacterial confirmation in such a case for at least six to eight weeks, even if one is eventually forthcoming. In such an instance I feel one should always keep in the back of one's mind the possibility that another disease may be the cause of the x-ray lesion, but it is perfectly reasonable to proceed to treat this patient with drugs.

MODERATOR ROGERS: *What drugs?*

DR. CHAVES: I would treat such a patient with a combination of isoniazid and p-amino salicylic acid.

MODERATOR ROGERS: *Would you put this patient to bed? Is bed rest still considered necessary for patients with proven minimal tuberculosis?*

DR. CHAVES: I would not put such a patient to bed. I don't believe it is necessary. In some instances I might even permit such a patient to continue on the job, provided the job is a good one and one which the patient can carry out without too much physical activity.

MODERATOR ROGERS: *That is a startling statement.*

DR. CHAVES: On the other hand, in some instances I would even insist that the patient go to a hospital because I would feel that a regimen of decreased activity that this disease requires could only be carried out outside of the patient's home environment. In other words, the indication for hospitalization of minimal tuberculosis is mainly a social one and is a matter for individualization.

MODERATOR ROGERS: *Dr. Woodward, I see you grinning here. How about Baltimore, how do you handle tuberculosis there? Do you put such patients to bed?*

DR. WOODWARD: I was grinning because I did not have to answer that question. Has there not been a study reported in this country with consideration given to the relative merits of ambulation versus bed rest? I would say that in Baltimore we are inclined to be conservative and advocate bed rest.

MODERATOR ROGERS: *Dr. Tompsett, would you care to comment on this?*

DR. TOMPSETT: Dr. Chaves knows so much more about this. I would like to agree with him. I don't have the experience but I certainly think that if this procedure is not followed now, it is something we shall be doing very soon.

MODERATOR ROGERS: *Dr. Chaves, I gather you hospitalize some patients with minimal tuberculosis whereas others you are content to treat on an ambulatory basis. What decides this for you?*

DR. CHAVES: For example, right now I am rather heavily involved in a community survey in the Bedford area of Brooklyn where we are picking up on the average about seven or eight active cases of tuberculosis per week, of which approximately 25 per cent are minimal. A number of minimal active cases from this source are referred to a local clinic for treatment where they are permitted to remain on the job or to continue their work as housewives, as the case may be. This has been done after a careful social history indicated that the home situation would permit reasonable cooperation on the part of the patient. But in most instances, in the population group that we are dealing with here, we have recommended, and have been successful in getting the patient with active minimal tuberculosis to go to a hospital because of inadequate home conditions, or a temperament or personality which we believed was not compatible with good control from the clinic.

MODERATOR ROGERS: *How about the practitioner who makes the discovery of active minimal tuberculosis, and proves it, in his private practice? Is this a disease which he should treat or should he refer it to someone with special training in tuberculosis?*

DR. CHAVES: The way you phrase the question, there is no doubt that the general practitioner can handle it because you have already handed him a proven case of minimal active tuberculosis. In other words, once a diagnosis has been established I think the management should be rather straightforward, namely, curtailing activity, continuing to check the sputum or gastric contents of the patient at regular intervals, periodic x-ray examination to follow the progress of the disease and long term chemotherapy.

MODERATOR ROGERS: *Let us be more specific—what is long term therapy?*

DR. CHAVES: For minimal active disease I would say at least one year. I have been tending to keep patients with minimal disease on treatment now for about 18 months.

MODERATOR ROGERS: *I notice again you advocate combined therapy. There has been much discussion about the use of more than one antituberculosis agent in minimal disease. What are your reasons for putting these patients on both isoniazid and p-amino salicylic acid and do you use streptomycin in the situation, or do you withhold it?*

DR. CHAVES: Actually, for minimal disease there is not nearly as good a case for combined therapy as there is for more advanced disease with cavitation. Isoniazid, whether it is combined with another drug or not, is quite adequate to take care of most patients with minimal tuberculosis. The reason I advocate the combination of isoniazid and p-amino salicylic acid is because in the more serious forms of disease, it has proven to be a better combination. Therefore I feel that it may be better medicine for a particularly stubborn type of minimal active disease.

MODERATOR ROGERS: *What about the more advanced disease? You mentioned combined therapy has proven superior. Is that because of the development of isoniazid resistance?*

DR. CHAVES: In the first place, there are three important drugs which are combined in various ways, for antituberculosis treatment. The three drugs are streptomycin, p-amino salicylic acid and isoniazid. They can be combined in any way: isoniazid and p-amino salicylic acid; isoniazid and streptomycin; streptomycin and PAS; or all three drugs can be used together. One can argue for any combination. One can argue against any combination. Would you want me to go through all those possibilities, or what?

MODERATOR ROGERS: *Is there any one "best" combination?*

DR. CHAVES: I think all of those combinations have their points. I personally believe that isoniazid, being the best of the three drugs, should be used when one has a fresh case of tuberculosis because it seems to me when a disease like tuberculosis is treated for the first time, one should use his best ammunition right off the bat, rather than saving it for some future emergency which may never show up.

MODERATOR ROGERS: *I would like to throw two more tough questions to you and then I will let you off the hook. What about the management of tuberculin converters? There has been much discussion about treating young children who convert from a negative to a positive tuberculin test, because we have highly effective therapy in isoniazid. What is your feeling on this?*

DR. CHAVES: This is a field that is full of controversy, as you know.

I think there is general agreement that when the tuberculin reaction of a child under the age of three converts, that child should be treated with isoniazid, either alone or in combination with PAS because the incidence of disseminated form of tuberculosis is so high in this age group.

MODERATOR ROGERS: *How high is it in this group?*

DR. CHAVES: It varies with the age. It falls right from birth but I would say that one may expect disseminated disease to occur in approximately 5 to 10 per cent of the converters under one year of age, and less frequently in the two and three year age group. But that is a significantly high percentage and it therefore seems worth while to treat all such children with isoniazid at the time of conversion.

As far as the treatment of converters in other age groups is concerned, I don't really think it merits much consideration. The arguments in favor are theoretical and speculative.

MODERATOR ROGERS: *I gather that when a medical student converts with no evidence of active disease you are inclined to withhold antibiotics.*

DR. CHAVES: I personally would treat them but I have been involved in some rather long arguments on that. As I said before I don't really believe there is conclusive evidence one way or another. If you believe there is a 1 per cent chance that a medical student who converts his tuberculin reaction might come down with significant pulmonary disease, by that I mean x-ray evidence of a lesion, and if you could prevent that by giving isoniazid, it is worth treating all 100 converters to save the one medical student coming down with the disease. The question is, can you do that? That has not really been shown.

MODERATOR ROGERS: *Just one more question: What is the status of BCG vaccination?*

DR. CHAVES: I think the questions you are asking are clear in my mind but because of widespread controversy I will give only my point of view. It is too bad we do not have another panelist with a contrary point of view! I believe the answer to the question as to the advisability of BCG vaccination is much easier now than it was a year ago, because there has been an excellent control study, by the British Medical Research Council in England, on the use of BCG which, to my way of thinking pretty convincingly shows that BCG has definite protective value against tuberculosis in adolescents. I say in adolescents because

that is the only age group that was studied. I think there is agreement that it has some value. The real question is, *how much* protection does BCG give the individual and is the amount of protection obtained worth the risks involved in vaccinating and the loss of the tuberculin test for diagnostic purposes.

In a nutshell, again, in areas where there is a lot of tuberculosis, BCG has a very definite place and where there is a small amount of tuberculosis it does not offer enough to warrant using it on a large scale.

MODERATOR ROGERS: *Very good! Thank you, Dr. Chaves!*

Would anyone else on the panel care to take issue with any of Dr. Chaves' carefully phrased answers? If not, we have some good questions here and I would like to make use of some of them. Dr. Woodward, what is the incidence of serious reactions to chloramphenicol?

DR. WOODWARD: I think the precautions that one takes with chloramphenicol are the precautions to be considered with most drugs. This question presumably refers to the blood dyscrasia problem. We have treated approximately 1600 patients with various specific infectious diseases. Blood counts were performed, before, during and after the administration of chloramphenicol for the *specific* illness. The antibiotic was given to typhoid fever patients with leukopenia of 1500 white blood cells per cu. mm. and to other patients with anemia of varying degree resulting from the specific disease. We have not encountered blood dyscrasias.

More recently at the Antibiotic Symposium in Washington, a paper described the results of long term chloramphenicol therapy in 2100 patients. Blood dyscrasias did not occur. I believe that chloramphenicol has caused blood dyscrasia in certain reported instances but seriously doubt that the true incidence is known. The hazard for important blood dyscrasia must be quite low when one considers the wide range of exposure to this antibiotic and the relatively small number of reported cases.

MODERATOR ROGERS: *You feel when you have specific indications like the diseases you have been discussing—*

DR. WOODWARD: I would give the antibiotic when specifically indicated. We do not withhold chloramphenicol. We prescribe it freely.

MODERATOR ROGERS: *Dr. Tompsett, I direct this one to you: How do you manage both urinary tract infections and more serious bac-*

teremic infections due to E. coli?

DR. TOMPSETT: It is somewhat unpredictable as to which drug is going to work. In such a case one has to rely on the sensitivity test, either the patient's response or *in vitro* sensitivity tests. By and large I feel that for a bona fide pyelonephritis due to E. coli, we would start the patient on tetracycline and follow through as is indicated thereafter. But there are several drugs which may be valuable in addition to tetracycline. The sulfonamide drugs of course are very valuable as is chloramphenicol. We generally reserve streptomycin for those persons who have bacteremic disease and who are more severely ill. In those patients we would sometimes use streptomycin.

MODERATOR ROGERS: *Is it your usual practice to start with tetracycline or sulfonamides, making subsequent changes on the basis of sensitivity studies or the patient's response?*

DR. TOMPSETT: The latter may be clearer and faster than the sensitivity test.

MODERATOR ROGERS: *Is it advisable to give B complex vitamins when using broad-spectrum antibiotics? Dr. Kilbourne, would you take a crack at that? Do you feel it is necessary?*

DR. KILBOURNE: I do not. There is some evidence which suggests that actual B complex deficiency can develop with long term antimicrobial therapy. I think that with our current methods nutritionists have difficulty detecting subclinical or borderline nutritional states so it is difficult to say that short term therapy has caused any important problem. My feeling would be that there is certainly no evidence for giving B complex except during the protracted administration of antimicrobials, particularly of the broad-spectrum variety.

MODERATOR ROGERS: *Would anybody argue with that? Dr. Woodward? Dr. Tompsett?*

We have time for just one more question: Is there any use in giving antihistamines with penicillin to prevent serious reactions? There is an addendum: How do you treat a severe penicillin reaction when it occurs in the physician's office or the patient's home?

Dr. Tompsett, do you think antihistamines are of any value in protecting the patient with a history of a previous penicillin reaction?

DR. TOMPSETT: I could answer that by saying, if the patient gives a history of previous reaction we don't like to use penicillin unless it is absolutely necessary. We avoid it then, when possible. If the patient

gives a history of reaction, however, and we feel that penicillin is required, we don't ordinarily give antihistamines until the patient again develops hypersensitivity, in which case we would. In other words, I don't think this should be done routinely. They are very useful in mild allergic reactions to penicillin.

MODERATOR ROGERS: *Dr. Kilbourne!*

DR. KILBOURNE: Antihistamines are not very helpful in drug fever and more important manifestations.

DR. TOMPSETT: I would say more than that! They are practically useless in patients with drug fever.

MODERATOR ROGERS: *The remainder of the question is: How do you treat a severe penicillin reaction when it occurs?*

DR. TOMPSETT: I think the main drug is epinephrine in severe allergic reactions. This can be followed by the use of Benadryl for carrying the patient along after this, but usually by the time one gets through giving the patient epinephrine, intramuscularly or at times intravenously—I am now talking about anaphylactic shock—the issue has been pretty well decided. Fairly general supportive measures may then be enough. I am not sure that we do much of value beyond the administration of epinephrine.

MODERATOR ROGERS: *In other words, you would try to avoid this situation whenever possible. I certainly agree that when anaphylaxis occurs treatment may be of very little moment.*

We have come to the end of our time. I would like to thank all the panelists and our audience for participating in the discussion this afternoon.